Malignant catarrhal fever (MCF)

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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

While a diagnosis on clinical and gross post-mortem examination may be possible in acute and more protracted cases presenting with the typical clinical signs of the disease, the wide spectrum of clinical manifestations that can develop frequently requires laboratory examination to establish a definitive diagnosis. Historically, the principle method for confirming a diagnosis was the detection of the characteristic histological changes of vasculitis, hyperplasia of lymphoid tissues and accumulations of lymphoid cells in non-lymphoid organs. The detection of these lesions in a variety of tissues particularly the brain, kidneys and liver provided a basis for reaching a diagnosis. However, with the development of molecular biological methodologies ante-mortem confirmation is now possible as is the identification of non-fatal infections. A history of contact with sheep or wildebeest or with pasture recently grazed by either of these species will generally support the diagnosis, but the possibilities of prolonged incubation periods and of transmission by aerosol or by fomite may make it difficult to establish this contact.

Clinical signs and pathology

The clinical and pathological changes associated with MCF resulting from infection with either AIHV-1 or OvHV-2 in susceptible animal species are similar and cannot be reliably differentiated.

The duration of the natural incubation period is often difficult to establish as the time of infection cannot be identified although there is good evidence that it can be very variable, ranging from two weeks to nine months. The course of the disease is also highly variable and ranges in individual animals from peracute or acute to chronic with more florid clinical signs developing in the more protracted cases which may die nine to ten days after the first clinical signs are noticed. In general, the disease in the more susceptible species follows an acute or peracute course. The peracute disease is characterized by rapid onset of depression and high fever followed by the development of diarrhoea, which in some cases may be haemorrhagic, with death occurring 12 to 24 hours after its onset. In all forms of the disease, the onset of signs is generally associated with the development of fever (rectal temperature of < 42 oC), inappetence, photophobia, lachrymation and a serous nasal exudate.
Epiphora and mucopurulent discharges from the eyes and nasal cavities

Blockage of the nares as a result of nasal exudate

The latter two progress to become profuse mucopurulent discharges. The ocular discharge may matt the hair on the face while the nasal exudate may, in time, result in blockage of the nares and difficult breathing. In lactating animals the milk yield drops. Characteristically, bilateral corneal opacity develops progressively from the periphery often to involve the whole cornea which may become oedematous and is accompanied by blindness. Corneal ulceration and hypopyon may be present.

Peripheral keratitis

Advanced keratitis with hypopyon

Salivation with hyperaemia of the oral epithelium may be an early sign. Erosions develop in the mucosa of the ventral surface of the tongue, hard palate, gums and, characteristically, the tips of the buccal papillae. In some cases skin lesions may develop but are often overlooked. These manifest as exanthema, exudation and encrustation of the areas concerned which are often restricted to the perineum, udder, teats, interdigital spaces and skin at the base of the horns and hooves.
Erosive and ulcerative interdigital dermatitis

Affected unpigmented skin is hyperaemic. Not infrequently the epithelium of the muzzle becomes severely encrusted, necrotic and may slough. The superficial lymph nodes are usually enlarged.

Visibly swollen pre-femoral lymph node

Neck extension to relieve discomfort associated with swollen lymph glands in the oro-pharyngeal region, blocked nares and conjunctival inflammation

Nervous signs such as hyperaesthesia, incoordination, nystagmus, behavioural changes and head pressing may be present in the absence of other clinical signs or as part of a more typical clinical picture. Some affected animals become aggressive.
Usually the outcome of MCF is fatal; however, mild cases of the SA-MCF were described. The latter observation was for a long time treated with scepticism but studies of some multiple case outbreaks using serological testing and PCR for OvHV-2 DNA have confirmed that such cases do occur. Recovery or mild disease may also occasionally occur in those animals in which the disease is caused by AlHV-1. However, the frequency with which this occurs is at present not clear.

The macroscopical and microscopical lesions caused by both AlHV-1 and OvHV-2 in all susceptible animal species are similar. They are generally widespread and may involve most organ systems. In animals in which the course of the disease was protracted, the carcass is emaciated and dehydrated. Apart from the lesions of the eyes, muzzle, external nasal orifices and skin which are clinically discernible, the mucous membranes of the upper and lower respiratory tract are congested and sometimes oedematous, may contain small haemorrhages, multiple foci of epithelial necrosis, erosions and ulcerations, as well as evidence of mucopurulent inflammation and pseudomembrane formation. The nasal passages, particularly between the turbinates may be partially blocked by exudate. A patchy bronchopneumonia may be present in animals which suffered from the more protracted disease.

The mucosa of the mouth may be hyperaemic and contain petechiae and ecchymoses and foci of epithelial necrosis, erosions and, in some, diphtheritic deposits.

Similar lesions may be found in the oesophagus, particularly its more cranial part, forestomachs and abomasum. In the latter organ, erosions and/or ulcers are frequently present particularly on the margins of the mucosal folds.
Ulcerations in the wall of the rumen

Erosions and ulcerations on the internal surface of the oesophagus

The small and large intestines may exhibit a catarrhal to haemorrhagic enteritis with their contents, particularly in the more acute cases, watery and blood-stained. Similar erosions or ulcerations to those in the abomasum may be present along the ridges of the mucosal rugae of the ileocaecal valve, caecum, colon and rectum. The intestinal lesions are generally more severe and widespread in deer.

The majority of lymph and haemolymph nodes are enlarged as a result of lymphoid hyperplasia, oedema and, in some, congestion. Some, particularly the submandibular and retropharyngeal, may
show foci of necrosis and haemorrhage. Slight splenomegaly may or may not be present. On cross section of the spleen, the white pulp is generally prominent.

The liver is usually slightly enlarged with diffuse greyish-yellow mottling. The wall of the gall bladder may be oedematous and contain petechiae and ecchymoses, and its mucosa a few small erosions.

In many cases the kidneys present characteristic changes. These are manifested by varying numbers of greyish-white foci one to five mm in diameter in the cortices, some of which may project above the renal surface and in some cases the presence of small scattered haemorrhages.

The mucosa and wall of the urinary bladder in most cases is oedematous and contains petechiae and ecchymoses in the mucosa and serosa and, occasionally, mucosal erosions or ulcers. Haematuria may be present.

The histopathological lesions, which have long formed the basis for confirming cases of MCF, are basically those of lymphoid hyperplasia, and vascular and epithelial lesions, the latter being associated with the infiltration or accumulation of cells mostly of the lymphocytic series, particularly lymphoblasts, into subepithelial tissues.
Segmental fibrinoid necrosis and lymphocyte infiltration in the wall of an artery

There is marked hyperplasia of lymphoblasts and reticuloendothelial cells in pre-existing lymphoid tissues as well as widespread interstitial accumulations of these cells in nonlymphoid organs such as kidneys, liver and lungs. The severity of the epithelial changes seems to correlate with that of the cellular infiltrations or accumulations in mucosae or dermis. The epithelial lesions may be present in all epithelial tissues and are characterized by inflammation, and erosion and/or ulcer development. Those in stratified squamous surfaces are also accompanied by acanthosis, parakeratosis and hyperkeratosis, vasculitis and haemorrhage.

The arterial and venous lesions are, characteristically, a fibrinoid vasculitis accompanied by the infiltration of lymphoblasts, lymphocytes and macrophages into the walls and adventitia of the vessels and perivascular spaces. Endothelial swelling may be present, and in the lumens there may be pavementing by lymphoid cells. Thrombosis is rare. The vascular lesions may be focal or segmental, and involve the full thickness of the wall of the vessel or be confined to one of the layers. They may occur throughout the body but are most prominent in the brain, meninges, carotid rete, liver, kidneys, lungs, and capsule and medulla of the adrenals as well as in those areas of the skin and alimentary tract which are grossly affected.

Marked hyperplasia of lymphoblasts occurs in the T cell-dependent areas of the interfollicular cortical and paracortical zones of lymph nodes. Evidence of necrosis of individual mature lymphocytes is usually present. Oedema, haemorrhages, focal areas of necrosis and vasculitis may be evident in the cortex and medulla. In the spleen, there is lymphoid cell hyperplasia and a depletion in the number of lymphocytes.

The mottling of the liver and the greyish-white foci in the cortices of the kidneys noted macroscopically are due to the accumulation of large numbers of lymphoid cells, mainly lymphoblasts and some macrophages in the portal tracts of the liver and interstitium of the kidneys, respectively. In the kidneys of some cases, thrombosis of arcuate or interlobular arteries gives rise to small infarcts.
In the brain, there may be a non-suppurative meningoencephalitis with perivascular lymphoid cuffing and a marked increase in the cellularity of the cerebrospinal fluid.

Consistent ocular findings include keratitis, uveitis, iridocyclitis, hypopyon, and vasculitis in most structures of the eye. Oedema, neovascularization, and mononuclear cell infiltration of the cornea arise at the limbus and spread centripetally. Erosion of the cornea may occur. The uveitis is frequently accompanied by the accumulation of fibrin, neutrophils and mononuclear cells in the anterior chamber of the eye and vitreous body.

The histopathological changes in the macroscopically-affected parts of the skin are characterized by a diffuse infiltration of all its layers by cells of the lymphoid series, oedema, vasculitis, haemorrhage, necrosis of epithelial cells, exudation and erosions, as well as hyperkeratosis, acanthosis and parakeratosis.

**Laboratory confirmation**

A variety of serological tests for detection of antibody in animals has been described, while recovery of virus in cell culture or identification of viral DNA by PCR amplification may be used to identify the virus. As most cattle infected with AlHV-1 die, the detection of antibody in clinically affected animals provides good supportive evidence. Antibody detection by neutralization assays using the cell-free WCII strain of virus is highly specific while assays, such as the IIFA test, are more rapid but cross reaction with antibody to bovine herpesvirus 4 (BHV-4) may confuse their interpretation.

Virus recovery of AlHV-1 in cell culture is achieved by co-cultivating either peripheral blood leukocytes or disaggregated cells from affected tissues with monolayer cell cultures of bovine or ovine origin. As virus can only be recovered from viable cells, tissue samples for virus isolation must be obtained either before or shortly after the death of the animal. These must be kept cool until processed in the laboratory. Virus cannot be recovered from frozen material.

The full sequence of the AlHV-1 genome has been published; thus primers for PCR can readily be designed for detecting viral DNA in peripheral blood leukocytes or affected tissues.

OvHV-2 has not been isolated, thus prior to the cloning and sequencing of a segment of viral DNA which allowed the design of an OvHV-2 specific PCR, confirmation of a diagnosis relied on histopathological examination or on the detection of antibody that cross reacted with AlHV-1. A CI-ELISA has been developed using a monoclonal antibody to AlHV-1 and has good specificity.

The PCR for OvHV-2 has been assessed as a diagnostic tool in several European countries, North America, Australia, New Zealand, Africa and Indonesia and has proved to be a robust, sensitive and specific indicator of infection. As viral DNA can be extracted from peripheral blood leukocytes confirmation of clinical cases is now possible. The application of the test to cattle involved in multiple case outbreaks has confirmed that up to 20 per cent of cases do recover and that mild, or even
inapparent infections, may also occur in up to ten per cent of those at risk. There is increasing evidence that the epidemiology of MCF is complex and is only now starting to be understood through the application of molecular techniques.

**Differential diagnosis**

The sporadic occurrence in cattle with signs and lesions typical of MCF and with identifiable contact with sheep or wildebeest is sufficient to reach a presumptive diagnosis. However, outbreaks affecting several animals do occur and the wide spectrum of clinical signs that may develop complicates the differential diagnosis.

Clinical signs similar to MCF may occur in many other conditions including mucosal disease, foot-and-mouth disease, lumpy skin disease and infectious bovine rhinotracheitis. In the more acute forms, in which diarrhoea is a prominent clinical sign, particularly in deer, yersiniosis presents a similar picture although, in general, this condition only affects animals under one year of age. In South Africa, severe disease associated with lachrymation, stomatitis, coronitis, sloughing of the skin of the teats and muzzle and, on occasion, diarrhoea has been recorded in cattle following infection with bluetongue virus and epizootic haemorrhagic disease virus. Therefore recourse to laboratory confirmation is generally required to reach a definitive diagnosis.